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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/729,653	12/04/2000	Biaoyang Lin	P-IS 4367	3087

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EXAMINER
DAVIS, MINH TAM B

ART UNIT	PAPER NUMBER
1642	16

DATE MAILED: 07/31/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/729,653	LIN, BIAOYANG	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 May 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *9-12,21-23 and 25* is/are pending in the application.

4a) Of the above claim(s) *21-23 and 25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *12,13* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's election with traverse of group II, claims 9-12, SEQ ID NO:2 in Paper No. 15 is acknowledged. The traversal is on the ground(s) that 1) the subject of group II is related to the methods of group IV, 2) a search of group II would result in the discovery of any art relevant to group II, and 3) there is no serious burden on the Examiner to search and examine both groups together. This is not found persuasive because groups II and IV are related as product and process, wherein the scope of group IV is different from the scope of group II. Further, the searches for the two groups are not co-extensive, and it would be a burden for the Examiner to examine the two groups together.

The requirement is still deemed proper and is therefore made FINAL.

Accordingly, claims 9-12, SEQ ID NO:2 are examined in the instant application.

OBJECTION

OK

Figure 5 is objected to because the panels are not labeled, and one would not know which panel is referred to in the figure legend of figure 5.

Claim Rejections - 35 USC § 112, SECOND PARAGRAPH

Claims 9-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 9-12 are indefinite for the use of the language "substantially" in claims 9-11. The term "substantially" in claims 9-11 is a relative term which renders the claim indefinite. The term "substantially" is not defined by the claims, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claim Rejections - 35 USC § 101, UTILITY

35 U.S.C. § 101 reads as follows:

"Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

Claims 9-12 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific asserted utility or a well established utility.

Claims 9-12 are drawn to a PAMP polypeptide, comprising substantially the amino acid sequence of SEQ ID NO:2 or the amino acid sequence of SEQ ID NO:2, and fragments thereof.

It is noted that a PAMP polypeptide, comprising "substantially" the amino acid sequence of SEQ ID NO:2 encompasses variants of SEQ ID NO:2.

The specification discloses that the PAMP polypeptide of SEQ ID NO:2 is a predicted polypeptide encoded by SEQ ID NO:1 (p.8, last paragraph and Example I, on pages 62-63), wherein SEQ ID NO: 1 is expressed in a prostate specific manner, in

both normal and cancer prostate tissues, and is androgen regulated when tested in prostate carcinoma cell line LNCaP (Examples II and III, on pages 63- 67 and figure 5). The specification further contemplates making antibodies specific for SEQ ID NO:2 (p.22), and the detection and treating prostate cancer, wherein expression of PAMP at a level 2-fold or more greater than the control expression level is an indiction of prostate neoplastic conditions (page 23), and wherein detection of PAMP outside of the prostate is indicative of metastasis of the cancerous prostate cells (p.25).

It is noted that there is no data however showing that the polynucleotide of SEQ ID NO:1 or the predicted encoded polypeptide of SEQ ID NO:2 and its variants are overexpressed in prostate cancer tissues as compared to normal prostate tissues, or that the polynucleotide of SEQ ID NO:1 or the predicted encoded polypeptide of SEQ ID NO:2 and its variants are detected outside of the prostate tissue.

The utility for the polypeptide of SEQ ID NO:2 is questionable, because one cannot predict that SEQ ID NO:2 and its variants actually exists in nature, and is expressed in a prostate-specific manner. Although the polynucleotide of SEQ ID NO:1 is expressed in prostate tumor and normal prostate, it is however unpredictable that the protein of SEQ ID NO:2 and its variants actually exist in nature, and is expressed in a prostate-specific manner, due to possible translation and post-translational negative control. It is well known in the art that regulation of mRNA translation is one of the major regulatory steps in the control of gene expression (Jansen, M et al, 1995, Pediatric Res, 37 (6): 681-686). Further, those of skill in the art recognize that expression of mRNA, specific for a tissue type, does not dictate nor predict the translation of such mRNA into

a polypeptide. For example, Alberts et al. (Molecular Biology of the Cell, 3rd edition, 1994, page 465) teach that translation of ferritin mRNA into ferritin polypeptide is blocked during periods of iron starvation. Likewise, if excess iron is available, the transferrin receptor mRNA is degraded and no transferrin receptor polypeptide is translated. Many other proteins are regulated at the translational level rather than the transcriptional level. For instance, Shantz and Pegg (Int J of Biochem and Cell Biol., 1999, Vol. 31, pp. 107-122) teach that ornithine decarboxylase is highly regulated in the cell at the level of translation and that translation of ornithine decarboxylase mRNA is dependent on the secondary structure of the mRNA and the availability of eIF-4E, which mediates translation initiation. McClean and Hill (Eur J of Cancer, 1993, vol. 29A, pp. 2243-2248) teach that p-glycoprotein can be overexpressed in CHO cells following exposure to radiation, without any concomitant overexpression of the p-glycoprotein mRNA. In addition, Fu et al (EMBO Journal, 1996, Vol. 15, pp. 4392-4401) teach that levels of p53 protein expression do not correlate with levels of p53 mRNA levels in blast cells taken from patients with acute myelogenous leukemia, said patients being without mutations in the p53 gene. Yokota, J et al (Oncogene, 1988,Vol.3, pp. 471-475) teach that the retinoblasma (RB) 115 kD protein is not detected in all nine cases of lung small-cell carcinoma, with either normal or abnormal size mRNA, whereas the RB protein is detected in three of four adenocarcinomas and all three squamous cell carcinomas and one of two large cell carcinomas expressing normal size RB mRNA. Thus, predictability of protein translation or the extent of translation is not solely contingent on mRNA expression due to the multitude of homeostatic factors affecting transcription and

translation. For the above reasons, one of skill in the art would not be able to predict if SEQ ID NO:536 is translated into a polypeptide expression product, or even if translated, whether it is overexpressed.

In addition, even if the claimed polypeptide of SEQ ID NO:2 is expressed in a prostate-specific manner, this prostate specificity would not constitute a specific utility, because said utility is shared by several other prostate specific polypeptides.

Further, even if the claimed polypeptide of SEQ ID NO:2 is expressed in a prostate-specific manner, it is unpredictable that using the claimed sequences of SEQ ID NO:2, detection of the presence of prostate cells in circulation would be useful for diagnostic and prognostic information about the presence in a subject of an invasive prostate tumor, because Gelmini S et al, 2001, Clin Chem Lab Med, 39(5): 385-91, teach that circulating prostate cells can be detected in peripheral blood of patients with clinically localized or advanced prostate carcinoma. Thus, one of would not have expected that the presence of prostate cells in circulation would be useful for distinguishing between localized and advanced or metastasized prostate carcinoma.

Further, even if the claimed polypeptide of SEQ ID NO:2 is expressed in a prostate-specific manner, it is unpredictable that one could use the claimed polypeptide for detecting metastasized prostate cells, because it is unpredictable that metastasized prostate cells still express the claimed sequence, because expression of a sequence could be lost during the progression toward metastasis. For example, Kibel, AS et al, 2000, J urol, 164(1): 192-6 teach that gene expression in the chromosomal region 12p12-13 is different in primary and metastatic cells, and that inactivation in the

chromosome region 12p12-13 occurs prior to metastasis. Ren, C et al, 1998, Cancer Res, 58(6): 1285-90, teach a loss of expression of lysyl oxidase mRNA during progression to metastasis. Gingrich, JR et al, 1996, Cancer res, 56(18): 4096-4102 teach a loss of normal E-cadherin expression as primary tumors become less differentiated and metastasize.

Further, the utility for the polypeptide of SEQ ID NO:2 and its variants is questionable, because neither the specification nor any art of record teaches what the polypeptide SEQ ID NO: 2 is, what it does do. They do not teach a utility for any of the fragments claimed; they do not teach a relationship to any specific diseases or establish any involvement in the etiology of any specific diseases. The asserted utilities for SEQ ID No: 2, such as production of antibodies apply to many unrelated polypeptide structures sequences. Therefore the asserted utilities are not considered "specific" utilities, i.e. they are not specific to SEQ ID NO: 2.

The specification essentially gives an invitation to experiment wherein the artisan is invited to elaborate a functional use for SEQ ID NO: 2. Because the claimed invention is not supported by a specific asserted utility for the reasons set forth, credibility of any utility cannot be assessed.

Claim Rejections - 35 USC § 112, FIRST PARAGRAPH, WRITTEN DESCRIPTION

The following is a quotation of the first paragraph of 35 USC 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 9, 11-12 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (*See Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 115).

Claim 9 is drawn a PAMP polypeptide, comprising "substantially" the amino acid sequence of SEQ ID NO:2.

Claims 11-12 are drawn to a PAMP polypeptide fragment, "comprising" at least eight or ten contiguous amino acids of residues 1 to 1074 of SEQ ID NO:2.

It is noted that a PAMP polypeptide, comprising "substantially" the amino acid sequence of SEQ ID NO:2 encompasses variants of SEQ ID NO:2.

. It is further noted that a PAMP polypeptide fragment, "comprising" at least eight or ten contiguous amino acids of residues 1 to 1074 of SEQ ID NO:2 encompasses unrelated sequences that share with SEQ ID NO:2 8 or 10 contiguous amino acids.

Although drawn specifically to the DNA art, the findings of *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412) are clearly relevant to the instant rejection. The court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

The specification discloses polypeptide variants that contain substitutions, additions, deletions of one or more conservative or non-conservative amino acid residues (p.20).

The claims 9, 11-12 however read on variants of SEQ ID NO:2 , wherein said variants have any type of substitution besides conservative substitution, at any amino acid, throughout the length of the polypeptide, as well as insertions and deletions. The

specification and the claims do not place any limit on which amino acid to be subjected to conservative or non-conservative substitution, the type of substitution besides conservative substitution, nor the type of amino acids replacing the original amino acids. In addition, the specification and all other pending claims do not place any limit on the number of amino acids that could be substituted. Although the specification discloses that the types of changes are routinely done in the art, the specification and the claims do not provide any guidance as to which, or how many original amino acid(s) to be substituted, or to which type of substitution besides conservative substitution, or which amino acids could be deleted or inserted so that the claimed polypeptide could function as contemplated. Structural features, that could distinguish the claimed variants from the polypeptide sequences known in the art are missing from the disclosure. No common structural attributes that identify the claimed variants are disclosed. In addition, no common functional attributes that identify the claimed variants are disclosed, because the function of a sequence could be abolished, even with substitution of only one amino acid of the polypeptide (Burgess et al. Journal of Cell Biology, 1990, 11: 2129-2138). The general knowledge and level of skill in the art do not supplement the omitted description, because specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the claimed variants, SEQ ID NO: 2 alone is insufficient to describe said variants. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of variants. Thus, applicant was not in possession of the claimed variants.

Thus, there is insufficient support of claims 9, 11-12 as provided by the Interim Written Description Guidelines published in the June 5, 1998 Federal Register at Volume 63, Number 114, pages 32639-32645.

Claim Rejections - 35 USC § 112, FIRST PARAGRAPH, ENABLEMENT

The following is a quotation of the first paragraph of 35 U.S.C. 112:

"The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention."

Claims 9-12 are rejected under 35 U.S.C. 112, first paragraph.

Claims 9, 10 are drawn a PAMP polypeptide, comprising "substantially" the amino acid sequence of SEQ ID NO:2 or a polypeptide of SEQ ID NO:2.

Claims 11-12 are drawn to a PAMP polypeptide fragment, comprising at least eight or ten contiguous amino acids of residues 1 to 1074 of SEQ ID NO:2.

1. Specifically, since the claimed invention is not supported by a well established utility for the reasons set forth in the rejection under 35 USC 101 above, one skilled in the art clearly would not know how to make/use the claimed invention.

2.. Moreover, claim 9 encompasses variants of SEQ ID NO:2.

Applicant not shown that variants of SEQ ID NO: 2 are capable of functioning as that which is being disclosed.

Protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, replacement of a single lysine residue at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein (Burgess et al. Journal of Cell Biology, 1990, 11: 2129-2138). In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen (Lazar et al. Molecular and Cell Biology, 1988, 8: 1247-1252). Similarly, it has been shown that aglycosylation of antibodies reduces the resistance of the antibodies to proteolytic degradation, while CH2 deletions increase the binding affinity of the antibodies (see Tao. et al. The Journal of Immunology, 1989, 143(8): 2595-2601, and Gillies et al. Human Antibodies and Hybridomas, 1990, 1(1): 47-54). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein.

In view of the above unpredictability, one of skill in the art would be forced into undue experimentation in order to perform the claimed invention as broadly as claimed.

In addition, although conservative subsititution would not destroy the biological function of a protein, the specification fails to disclose which amino acid(s) would be subjected to conservative substitution. In the absence of a source of method of making such variants, one of skill in the art would be forced into undue experimentation to practice the claimed invention as broadly as claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

1. Claims 9, 11-12 are rejected under 35 U.S.C. 102(a) as being anticipated by Nagase T et al, or Kawakami T et al, Genbank Sequence Database (Accession No: Q9HCD4 and Q9H5S0, respectively), National Center for Biotechnology Information, National Library of Medicine, Bethesda, Maryland, publicly available on 2000.

Claim 9 is drawn a PAMP polypeptide, comprising "substantially" the amino acid sequence of SEQ ID NO:2.

Claims 11-12 are drawn to a PAMP polypeptide fragment, "comprising" at least eight or ten contiguous amino acids of residues 1 to 1074 of SEQ ID NO:2.

Nagase T et al teach a sequence which is 99.8% similar to the claimed SEQ ID NO:2, from amino acid 375 to 1279, under MPSRCH sequence homology search (MPSRCH search report, us-09-729653-2.rspt, pages 1-2).

Kawakami T et al teach a sequence which is 99.3% similar to the claimed SEQ ID NO:2, from amino acid 41-492, under MPSRCH sequence homology search (MPSRCH search report, us-09-729653-2.rspt, page 3).

Given the polypeptide sequence taught by Nagase T et al, or Kawakami T et al, one of ordinary skill in the art would immediately envision the claimed polypeptide or fragments thereof.

2. Claims 9 and 11 are rejected under 35 U.S.C. 102(b) as being anticipated by Steward, C A, Genbank Sequence Database (Accession No: 046018), National Center for Biotechnology Information, National Library of Medicine, Bethesda, Maryland, publicly available on 1998.

Claim 9 is drawn a PAMP polypeptide, comprising "substantially" the amino acid sequence of SEQ ID NO:2.

Claim 11 is drawn to a PAMP polypeptide fragment, "comprising" at least eight contiguous amino acids of residues 1 to 1074 of SEQ ID NO:2.

Steward, C A teaches a sequence which is 45% similar to the claimed SEQ ID NO:2, from amino acid 724 to 1228, under MPSRCH sequence homology search (MPSRCH search report, us-09-729653-2.rspt, page 4).

Given the polypeptide sequence taught by Steward, C A, one of ordinary skill in the art would immediately envision the claimed polypeptide or fragments thereof.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 703-305-2008. The examiner can normally be reached on 9:30AM-4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, ANTHONY CAPUTA can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0916.

MINH TAM DAVIS

July 19, 2002

SUSAN UNGAR, PH.D
PRIMARY EXAMINER